In Situ Male Breast Carcinoma in the Surveillance, Epidemiology, and End Results Database of the National Cancer Institute

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BACKGROUND. In situ breast carcinoma is not so well characterized for men as for women.

METHODS. Therefore, the authors of the current study compared male and female in situ and invasive breast carcinomas in the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute to document these patterns.

RESULTS. In situ breast carcinomas composed 9.4% of all male (n = 280 of 2984) and 11.9% of all female breast carcinomas (n = 53,928 of 454,405) during the years 1973–2001. In situ rates rose 123% for men and 555% for women over this time period; whereas distant disease rates fell for both genders. Median ages at diagnosis were 62 years for in situ and 68 years for invasive breast carcinoma among men, compared with 58 years for in situ and 62 years for invasive breast carcinoma among women. Papillary in situ and invasive architectural types were more common among men than women. In contrast, lobular tumors were more common among women than men. Breast cancer-specific survival was similar among men and women, whereas overall survival was worse for men than women.

CONCLUSION. In situ male breast carcinoma is a rare disease, occurring at older ages and with different architectural types than its more common female counterpart. Gender-specific histopathologic differences probably reflect anatomic differences among the normal female and vestigial male breast. Rising in situ male breast carcinoma incidence rates over the past three decades suggest earlier detection over time, irrespective of mammography, because men do not participate in routine screening mammography. Worse overall survival for men than women possibly results from age-dependent comorbid illnesses. ***Cancer*** **2005;104: 1733–41.** *Published 2005 by the American Cancer Society.**

KEYWORDS: male breast carcinoma, cancer in situ, hormone receptor expression, prognostic factors.

In a previous study,[1] we observed distinct age-specific incidence rate patterns among women with in situ and invasive breast carcinomas, noting that in situ disease was more like estrogen receptor (ER)-negative than ER-positive invasive breast carcinomas. We speculated that men might demonstrate similar in situ and invasive incidence rates; but these patterns have not been documented for male breast carcinoma. Moreover, previous in situ male breast carcinoma studies have been mostly small case-reports and/or hospital series, using frequency rather than population-based rates.

We, therefore, examined population-based patterns among men with in situ breast carcinoma in the large-scale Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer

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Institute (NCI) to define these patterns and to develop etiologic hypotheses. To our knowledge, this is the largest single series of in situ male breast carcinoma, nearly doubling the previous worldwide experience of less than 200 patients.[2,3]

MATERIALS AND METHODS

We used the NCI's SEER Cancer Incidence Public-Use database (November 2003) to analyze male and female in situ and invasive breast carcinomas (InvBC) diagnosed during the years 1973 to 2001.[4] The SEER program provided overlapping 9 and 12 Registry Databases. The 9 Registry Database collected 457,389 breast carcinoma cases (male = 2984 and female = 454,405) during the years 1973–2001 from SEER's original catchment regions, including registries in Atlanta (GA), Connecticut, Detroit (MI), Hawaii, Iowa, New Mexico, San Francisco–Oakland (CA), Seattle–Puget Sound (WA), and Utah. The 12 Registry Database collected 291,333 breast carcinoma cases (male = 1855 and female = 289,478) breast carcinoma cases during the years 1992–2001 from SEER's original 9 registries plus Los Angeles (CA), San Jose–Monterey (CA), and the Alaskan Native Tumor registries. Although operative for fewer years than the 9 Registry Database, the 12 Registry Database provided more information for tumor characteristics and hormone receptor expression. For example, SEER did not collect information concerning tumor size, axillary lymph node status, or histologic grade in a way that could be linked to the American Joint Commission on Cancer (AJCC) carcinoma staging system until 1988, and SEER did not collect data regarding hormone receptor expression until 1990. We, therefore, used the SEER 9 Registry database for long-term temporal trends and the SEER 12 Registry database for cross-sectional descriptive statistics, age-specific incidence rates, breast carcinoma and overall survival. There were $n = 280$ in situ male breast carcinoma cases in the SEER 9 database and $n = 209$ in situ male breast carcinoma cases in the SEER 12 database.

Incident patient demographics and tumor characteristics were age, tumor size, race, historic SEER stage, histopathologic subtype, grade, estrogen receptor (ER) expression, and progesterone receptor (PR) expression. Data were stratified by age $<$ 50 years and $\geq$ 50 years to simulate rates occurring before and after menopause, respectively. Historic SEER stage included in situ, local InvBC, regional InvBC, and distant InvBC. All noninvasive tumors were coded as in situ lesions. Local disease referred to InvBC confined entirely within the breast. Regional disease referred to InvBC extending beyond the confines of the breast into the surrounding chest wall and/or regional axillary lymph nodes. Distant disease included InvBC with systemic metastases.

SEER used codes from the International Classification of Diseases for Oncology 3rd edition (ICD-O-3) to defined histopathologic subtypes for in situ (behavior code/2) and InvBC (behavior code/3):[5,6] In this analysis, we included only those codes for breast epithelial carcinomas. Codes for sarcomas and/or lymphomas of the breast were excluded: morphology codes were duct noncomedo carcinoma (ICD-O-3 code 8500), including duct carcinoma of no special type or not otherwise specified (NST or NOS); duct comedocarcinoma (ICD-O-3 code 8501); Paget disease (ICD-O-3 codes 8540-8543); tubular carcinoma (ICD-O-3 codes 8211); lobular carcinoma (ICD-O-3 codes 8520-8521); medullary carcinoma (ICD-O-3 codes 8510-8512); papillary carcinoma (ICD-O-3 codes 8050, 8260, 8503); mucinous carcinoma (ICD-O-3 codes 8480-8481); other or unknown included all other ICD-O-3 codes.

Tumor characteristics were arbitrarily categorized as low risk (relatively favorable) or high risk (relatively unfavorable) categories. Low-risk or high-risk tumor characteristics, respectively, were size $\leq$ 2.0 or $>$ 2.0 cm in diameter, negative or positive axillary lymph nodes (LN negative or positive), low or high grade, ER-positive or ER-negative expression, and PR-positive or PR-negative expression. Histologic grading conformed to ICD-O-3 convention. We combined Grade I (well differentiated) with Grade II (moderately differentiated) into low grade and Grade III (poorly differentiated) with Grade IV (undifferentiated) into high grade. Because no centralized laboratory was used to determine hormone receptor status, each SEER registry recorded ERs and PRs as positive, negative, missing, borderline, or unknown. We combined missing, borderline, and unknown data into one group, which we designated other or unknown.

Incidence rates with standard errors (*SE*) were calculated using SEER stat 5.2.2, age-adjusted to the 2000 U.S. standard and expressed as a ratio with 100,000 man years or woman years. Relative risks for tumor characteristics were expressed as incidence rate ratios (RR), where a high-risk characteristic was compared with a low-risk characteristic with an assigned RR of 1.0. Ninety-five percent confidence limits (95% CI) were calculated as described by Miettinen and Nurminen.[7] Age-specific incidence rates were charted on a log–log scale.[8,9] Age-specific incidence rates were stratified by behavior (in situ vs. InvBC) and ER-positive vs. ER-negative expression. We used the Kaplan–Meier product-limit method to calculate breast carcinoma-specific survival and overall (all causes) survival for each SEER historic stage.[10] Cumulative survival

TABLE 1
Age-Adjusted Breast Carcinoma Incidence Rates per 1000,000 Person-Years by Gender SEER 9 Registry Databases (1975–1980 through 1997–2001)

	Male breast carcinoma					
Year	Total rate	In situ rate	Invasive rate	Local rate	Regional rate	Distant rate
1975–1980	1.017	0.065	0.952	0.455	0.351	0.090
1981–1986	1.046	0.079	0.967	0.418	0.433	0.081
1987–1991	1.223	0.118	1.105	0.463	0.505	0.073
1992–1996	1.234	0.112	1.122	0.550	0.430	0.096
1997–2001	1.313	0.145	1.168	0.622	0.464	0.053
percentage change	29%	123%	23%	37%	32%	−41%
	Female breast carcinoma					
	Total rate	In situ rate	Invasive rate	Local rate	Regional rate	Distant rate
1975–1980	106.986	4.863	102.123	49.393	40.375	7.463
1981–1986	123.668	8.421	115.247	58.758	43.707	7.622
1987–1991	149.678	18.090	131.588	78.111	40.802	7.636
1992–1996	154.422	22.963	131.459	83.229	36.445	7.372
1997–2001	169.344	31.858	137.487	87.688	39.078	7.483
percentage change	58%	555%	35%	78%	−3%	0%

Total: in situ plus invasive; Invasive: overall invasive; Local: local invasive; Regional: regional invasive; Distant: distant invasive.

curves for each SEER historic stage were stratified by gender and then were compared with the two-sided log-rank test.[11]

RESULTS

The 9 original SEER registries collected 457,389 breast carcinoma cases, 0.7% of which were male (n = 2984) and 99.3 % were female (n = 454,405), diagnosed during the years 1973–2001. In situ disease composed 9.4% (280 of 2,984) of all male breast carcinomas and 11.9% (53,928 of 454,405) of all female breast carcinomas.

From 1975 (the first year with complete data for SEER's 9 original registries) through 2001, total (in situ plus invasive) breast carcinoma incidence rates increased 29% for men and 58% for women (Table 1, Fig. 1), based upon two 6-year (1975–1980 and 1981–1986) and three 5-year time periods (1987–1991, 1992–1996, and 1997–2001). There were temporal increases for in situ and local InvBC with decreases in regional InvBC and distant InvBC among both genders. For example and from 1975 to 2001, in situ rates rose 123% and 555% among men and women, respectively, whereas local InvBC increased more modestly, 37% and 78% for men and women, respectively (Table 1). Regional and distant temporal trends were more variable than

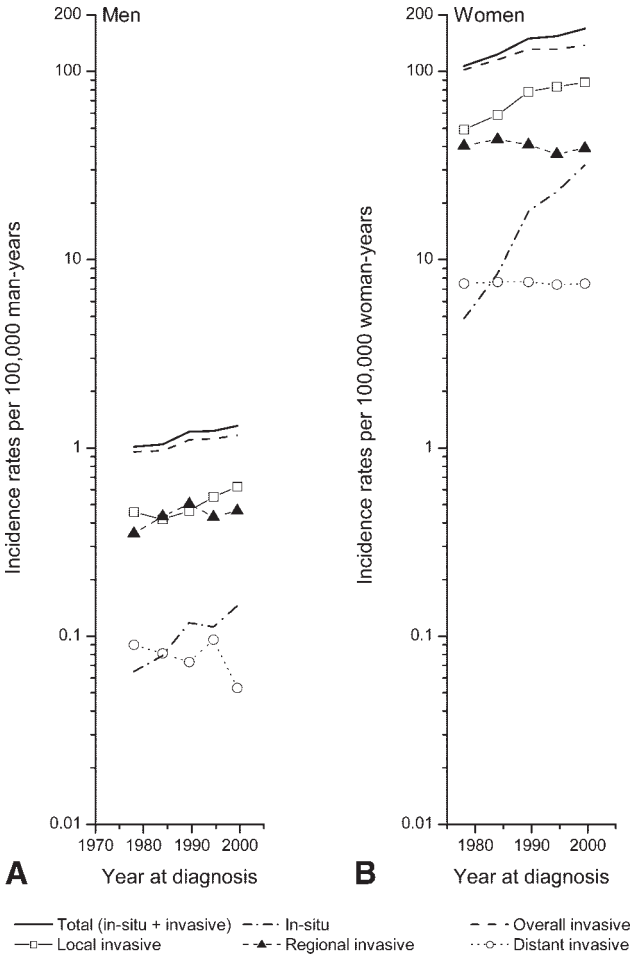

FIGURE 1. Age-adjusted breast carcinoma incidence trends by gender and stage for the SEER 9 Registry Database during the years 1975 (the first year with complete data for the 9 original SEER registries) to 2001, based upon two 6-year and three 5-year time periods, respectively. The time periods were 1975–1980, 1981–1986, 1987–1991, 1992–1996, and 1997–2001. (A) Men and (B) Women.

in situ and local disease rates, but in contrast to early stage disease, late-stage tumors appeared to have a downward trend for both genders. Among men, regional InvBC increased initially from 1975 to 1987 then decreased 8.1% from 1987–1991 (0.505 per 100,000) to 1997–2001 (0.464 per 100,000) while distant InvBC decreased 41% from 1975 to 2001. Among women, regional InvBC increased until 1981 then fell 16% from 1981–1986 (43.707 per 100,000) to 1992–1996 (36.445 per 100,000), and distant InvBC fell 2% from 1987–1991 to 1997–2001.

Patient demographic and tumor characteristics were stratified by in situ and by InvBC for men (Table 2) and for women (Table 3) for SEER's 12 Registry Database (1992–2001). Median ages at diagnosis were 62 years for in situ and 68 years for InvBC among men,

TABLE 2
Descriptive Statistics for Certain Tumor Features in the SEER 12 Registry Database among Male Breast Carcinoma Patients Diagnosed during 1992–2001

Variables	Carcinoma in situ						Invasive breast carcinoma (InvBC)					
Total *N* = 1855	209						1646					
% of total cases	11.3						88.7					
Rate (SE)	0.1 (0.10)						0.2 (0.03)					
Median age	62 yrs						68 yrs					
Median tumor size	1.0 cm						2.0 cm					
Demographics	***N***	**%**	**Rate**	***SE***	***RR***	***95% CI***	***N***	**%**	**Rate**	***SE***	***RR***	**95% CI**
Age in yrs												
< 50	41	19.6	0.030	0.005	1.00		188	11.4	0.144	0.011	1.00	
50–59	51	24.4	0.291	0.041	9.70	6.32–14.88	296	18.0	1.686	0.098	11.71	9.70–14.13
60–69	47	22.5	0.405	0.059	13.50	8.75–20.83	430	26.1	3.701	0.179	25.70	21.53–30.68
70–79	51	24.4	0.625	0.088	20.83	13.58–31.95	459	27.9	5.677	0.265	39.42	33.08–46.99
≥ 80	19	9.1	0.523	0.121	17.43	9.97–30.49	273	16.6	7.818	0.477	54.29	44.82–65.76
Race												
White	174	83.3	0.140	0.011	1.00		1342	81.5	1.152	0.032	1.00	
Black	19	9.1	0.158	0.039	1.13	0.68–1.88	196	11.9	1.822	0.140	1.58	1.35–1.86
Other	10	4.8					87	5.3				
Unknown	6	2.9					21	1.3				
Pathology												
Morphology												
Duct (noncomedo)	102	48.8	0.067	0.007	1.00		1244	75.6	0.872	0.025	1.00	
Duct (comedo)	12	5.7	0.008	0.002	0.12	0.07–0.20	7	0.4	0.005	0.002	0.01	0.00–0.01
Paget disease	1	0.5	0.001	0.001	0.01	0.00–0.11	29	1.8	0.022	0.004	0.03	0.02–0.04
Tubular	0	0.0	0.000	NA	NA	NA	7	0.4	0.005	0.002	0.01	0.00–0.01
Lobular	6	2.9	0.004	0.002	0.06	0.02–0.16	25	1.5	0.018	0.004	0.02	0.01–0.03
Medullary	0	0.0	0.000	NA	NA	NA	9	0.5	0.005	0.002	0.01	0.00–0.01
Papillary	49	23.4	0.033	0.005	0.49	0.34–0.71	45	2.7	0.031	0.005	0.04	0.03–0.05
Mucinous	0	0.0	0.000	NA	NA	NA	34	2.1	0.024	0.004	0.03	0.02–0.04
Other or unknown	39	18.7					246	14.9				
Nuclear grade												
Low	72	34.4	0.048	0.006	1.00		831	50.5	0.584	0.021	1.00	
High	23	11.0	0.015	0.003	0.31	0.20–0.50	517	31.4	0.363	0.016	0.62	0.56–0.69
Other or unknown	114	54.5					298	18.1				
Hormone receptors												
ER												
ER positive	21	10.0	0.014	0.003	1.00		1076	65.4	0.755	0.023	1.00	
ER negative	4	1.9	0.003	0.001	0.21	0.10–0.47	108	6.6	0.072	0.007	0.10	0.08–0.12
Other or unknown	184	88.0					462	28.1				
PR												
PR positive	21	10.0	0.014	0.003	1.00		915	55.6	0.645	0.022	1.00	
PR negative	3	1.4	0.002	0.001	0.14	0.05–0.41	225	13.7	0.152	0.010	0.24	0.20–0.27
Other or unknown	185	88.5					506	30.7				

N: sample size; Rate: age-adjusted (2000 U.S. standard) incidence rate per 100,000-years; RR: rate ratio where a high-risk characteristic is compared with a low-risk characteristic with an assigned RR of 1.0.

compared with 58 years for in situ and 62 years for InvBC among women. Median tumor sizes at diagnosis were slightly larger for men than for women for both in situ and InvBC.

Compared with age at diagnosis ≤ 50 years, incidence rates and RRs for men peaked between ages 70–79 years for in situ (RR =20.83; 95% CI = 13.58–31.95) and ≥ 80 years for InvBC (RR = 54.29; 95% CI = 44.82–65.76), respectively. In situ (RR = 8.06) and InvBC rate ratios (RR = 11.08) for women both peaked between ages 70–79 years. RR for Black versus White race was greater than 1.00 among men and less than 1.00 among women for both in situ and InvBC.

Although there were no cases of tubular, medullary, or mucinous in situ male breast carcinomas, every histopathologic subtype of invasive breast carcinoma was observed among men (Table 2). Conversely, every histopathologic subtype was noted for both in

TABLE 3
Descriptive Statistics for Certain Tumor Features in the SEER 12 Registry Database among Female Breast Carcinoma Patients Diagnosed during 1992–2001

Variable	Carcinoma in-situ						Invasive breast carcinoma (InvBC)					
Total *N* = 289,487	46,929						242,549					
% of total cases	16.2						83.8					
Rate (SE)	26.1 (0.12)						132.5 (0.27)					
Median age	58 yrs						62 yrs					
Median tumor size	0.8 cm						1.6 cm					
Demographics	***N***	**%**	**Rate**	**SE**	**RR**	**95% CI**	***N***	**%**	**Rate**	**SE**	**RR**	**95% CI**
Age in yrs												
< 50	12,742	27.2	9.68	0.086	1.00		56,899	23.5	42.58	0.179	1.00	
50–59	12,370	26.4	66.91	0.602	6.91	6.74–7.08	51,756	21.3	279.94	1.231	6.57	6.50–6.65
60–69	10,219	21.8	76.48	0.757	7.90	7.70–8.11	51,982	21.4	388.93	1.707	9.13	9.03–9.24
70–79	8603	18.3	78.07	0.842	8.06	7.85–8.29	51,957	21.4	471.69	2.069	11.08	10.95–11.21
80+	2995	6.4	43.77	0.800	4.52	4.34–4.71	29,955	12.4	433.04	2.504	10.17	10.03–10.31
Race												
White	38,382	81.8	26.89	0.138	1.00		202,824	83.6	138.33	0.309	1.00	
Black	3913	8.3	23.43	0.378	0.87	0.84–0.90	20,320	8.4	120.29	0.854	0.87	0.86–0.88
Other	4090	8.7					18,053	7.4				
Unknown	544	1.2					1352	0.6				
Pathology												
Morphology												
Duct (noncomedo)	23,160	49.4	12.85	0.085	1.00		167,269	69.0	91.58	0.225	1.00	
Duct (comedo)	8660	18.5	4.81	0.052	0.37	0.37–0.38	4392	1.8	2.43	0.037	0.03	0.03–0.03
Paget disease	167	0.4	0.09	0.007	0.01	0.01–0.01	1873	0.8	1.02	0.024	0.01	0.01–0.01
Tubular	15	0.0	0.01	0.002	0.00	0.00–0.00	3877	1.6	2.15	0.035	0.02	0.02–0.02
Lobular	5450	11.6	3.08	0.042	0.24	0.23–0.25	20,057	8.3	10.93	0.077	0.12	0.12–0.12
Medullary	3	0.0	0.00	0.001	0.00	0.00–0.00	2508	1.0	1.38	0.028	0.02	0.01–0.02
Papillary	2901	6.2	1.59	0.030	0.12	0.12–0.13	1550	0.6	0.83	0.021	0.01	0.01–0.01
Mucinous	19	0.0	0.01	0.002	0.00	0.00–0.00	6343	2.6	3.39	0.043	0.04	0.04–0.04
Other or unknown	6554	14.0					34,680	14.3				
Nuclear grade												
Low	12,764	27.2	7.09	0.063	1.00		118,321	48.8	64.77	0.189	1.00	
High	10,046	21.4	5.60	0.056	0.79	0.77–0.81	78,805	32.5	43.17	0.154	0.67	0.66–0.67
Other or unknown	24,119	51.4					45,423	18.7				
Hormone receptors												
ER												
ER positive	4727	10.1	2.62	0.038	1.00		145,403	59.9	79.54	0.209	1.00	
ER negative	1464	3.1	0.81	0.021	0.31	0.29–0.33	43,586	18.0	23.98	0.115	0.30	0.30–0.30
Other or unknown	40,738	86.8					53,560	22.1				
PR												
PR positive	4081	8.7	2.26	0.035	1.00		121,698	50.2	66.64	0.192	1.00	
PR negative	1908	4.1	1.06	0.024	0.47	0.44–0.49	60,926	25.1	33.39	0.136	0.50	0.50–0.51
Other or unknown	40,940	87.2					59,925	24.7				

N: sample size; Rate: age-adjusted (2000 U.S. standard) incidence rate per 100,000 woman-years; RR: rate ratio where a high-risk characteristic is compared with a low-risk characteristic with an assigned RR of 1.0.

situ and invasive breast carcinomas among women (Table 3). Ductal noncomedo carcinoma was the predominant histopathologic subtype for both men (in situ, 48.8%; InvBC, 75.6%) and women (in situ, 49.4%; InvBC, 69.0%). Lobular carcinomas composed a smaller fraction of breast carcinoma for men (in situ, 2.9%; InvBC, 1.5%) than for women (in situ, 11.6%; InvBC, 8.3%). Conversely, papillary carcinomas were a larger fraction of breast carcinoma for men (in situ, 23.4%; InvBC, 2.7%) than for women (in situ, 6.2%; InvBC, 0.6%). Unlike all other morphologic subtypes, incidence rates for comedocarcinomas and papillary carcinomas were greater for in situ than for InvBC among both genders.

Rates and RR for grade and hormone receptor expression must be interpreted with caution because of missing data, especially for in situ lesions. With that said, tumor characteristics were generally more favor-

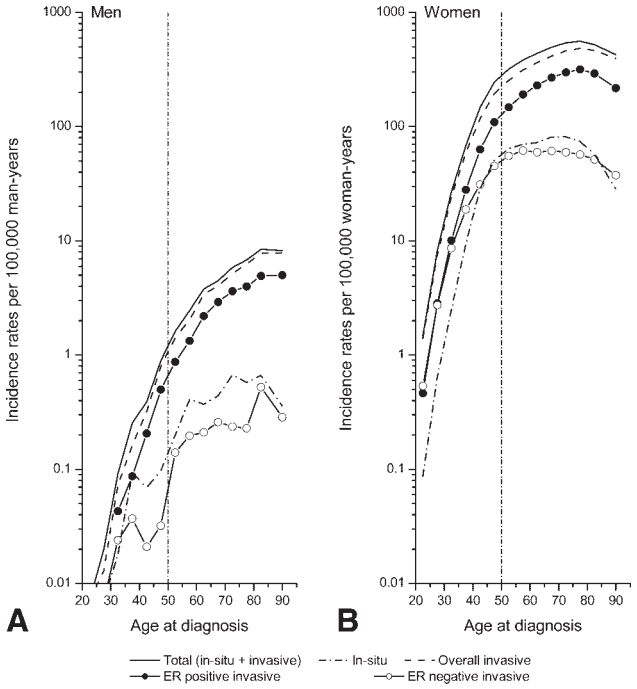

FIGURE 2. Age-specific breast carcinoma incidence rates by estrogen receptor (ER) expression among men and women in the SEER 12 Registry Database during the years 1992–2001.

able for men than for women. For example, in situ RR for high grade compared with low grade was lower for men (RR=0.31) than for women (RR = 0.79). Likewise, InvBC RR for high grade compared with low grade was slightly less for men (RR = 0.62) than for women (RR = 0.67). We noted similar patterns for hormone receptor expression.

Age-specific incidence rate curves for men and for women are shown in Figure 2 for the SEER 12 Registry Database (1992–2001). Age-specific rates for total breast carcinoma and for InvBC overall among men generally increased steadily with advancing age, whereas among women they increased rapidly until age 50 years then continued to rise at slower rates, with decreases at the oldest ages. Rates for ER-positive InvBC tumors paralleled rates for InvBC overall among both sexes. Among men, rates for ER-negative InvBC increased rapidly until age 50 years, and then continued to rise at a slower rate. Among women, rates for ER-negative InvBC tumors increased rapidly until age 50 years, and then flattened and fell. For both sexes, rates for in situ tumors overall were parallel to rates for ER-negative InvBC.

Historic SEER stage-specific breast carcinoma (figure 3) and overall survival (figure 4) were stratified by gender for the SEER 12 Registry Database (1992–2001). Breast carcinoma-specific survival was similar among men and women for all stages. Conversely, overall (all cause) survival was worse among men compared to women for in situ, local InvBC, and regional InvBC, but not for distant InvBC.

DISCUSSION

In situ breast carcinoma is not as well documented among men as it is among women, probably because of its rarity and lack of routine surveillance. For example, breast carcinoma is 100 times less common in men than women, and in situ lesions compose a smaller fraction of male than female breast carcinomas (11% vs. 16%, Tables 2 and 3, respectively).[3,12] Moreover, most in situ female breast carcinomas are screen-derived,[13] whereas men do not participate in routine screening mammography.

Giordano et al. recently reported a 26% increase in male breast carcinoma incidence overall, based upon 5-year increments and including all tumor stages.[14] The explanation for this increase was unclear. Notably, our Figure 1 showed temporal increases for in situ and local InvBC with decreases in regional InvBC and distant InvBC, among men as well as women. So, the overall male breast carcinoma trend reported by Giordano et al. appears to be predominantly occurring in early stage tumors.[15,16] The reciprocal divergence between early stage and late-stage disease rates suggests earlier detection over time[17] for both male and female breast carcinomas.

Whereas the rapid rise for in situ female breast carcinomas during the 1980s undoubtedly resulted from increases in screened-derived occult or "asymptomatic" tumors,[13] the rise for in situ male breast carcinomas could not be attributed to screening mammography because men do not participate in routine screening programs. However, heightened awareness of breast carcinoma in general might have resulted in earlier detection of "symptomatic" male in situ and localized tumors because of easier detection of small lesions in men than in women because men have less breast tissue.[18,19] These findings for in situ breast carcinoma among men suggest that some of the increase for in situ breast carcinoma among women may also be attributed to factors other than screening mammography.

Among men, in situ and InvBC were more common in Blacks than in Whites with RRs of 1.13 and 1.58, respectively (Table 2); whereas among women, in situ and InvBC were more common in Whites than in Blacks with RRs of 0.87 and 0.87, respectively (Table 3).[20] The morphologic spectrum for in situ breast carcinoma also was markedly different among men and women. Comedo, tubular, lobular, medullary, and mucinous in situ lesions were either less common or

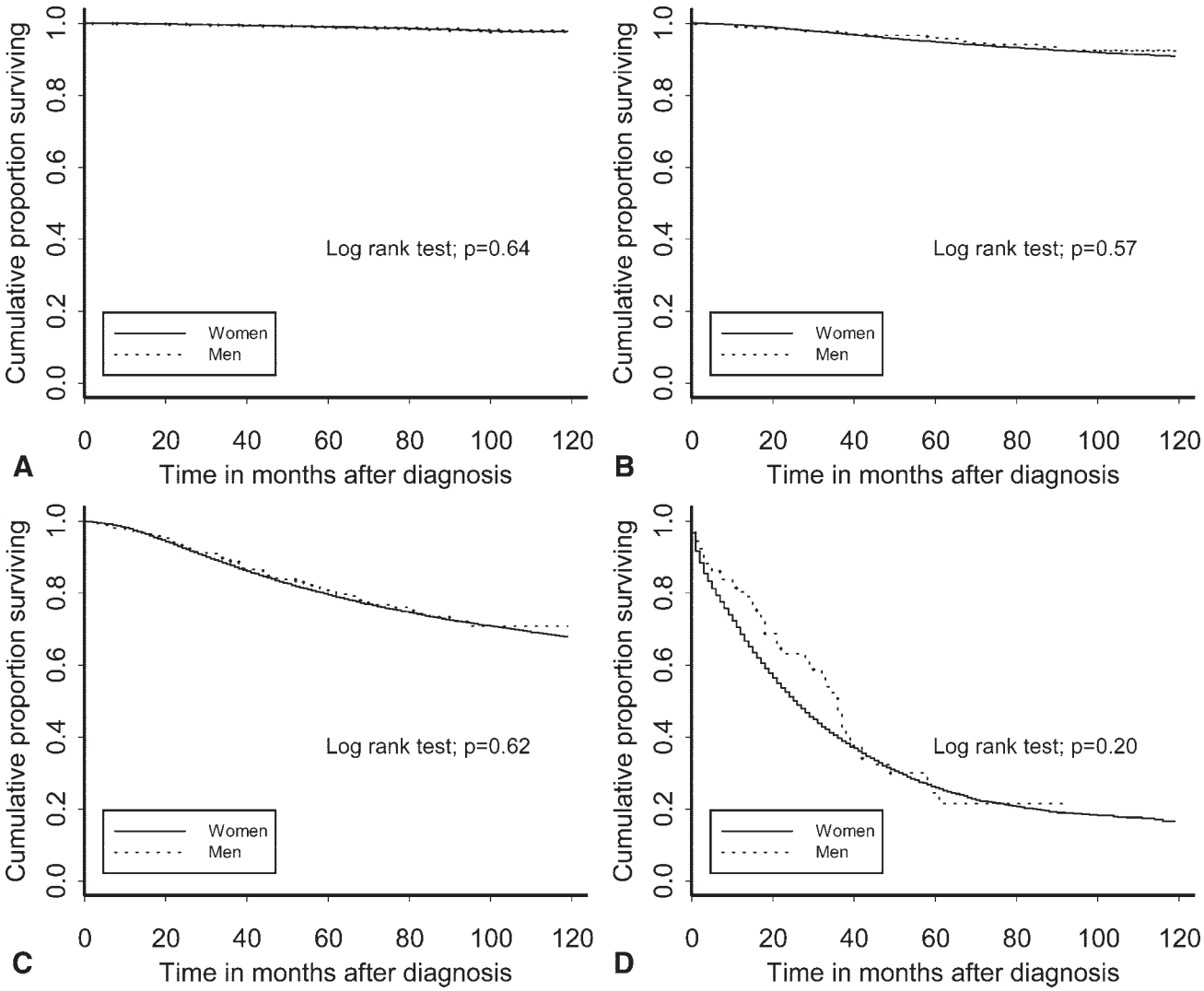

FIGURE 3. SEER historic stage-specific actuarial breast carcinoma survival by gender for the SEER 12 Registry Database during the years 1992–2001. (A) In situ breast carcinomas; (B) Local invasive breast carcinoma; (C) Regional invasive breast carcinoma; (D) Distant invasive breast carcinoma.

absent among men compared to women, whereas in situ papillary lesions were relatively more common among men than women.

Gender-related differences for certain morphologic types of breast carcinoma probably reflected anatomic and hormonal differences among men and women. For example, the majority of female breast carcinomas are thought to arise from the terminal duct lobular unit (TDLU),[21] which differentiates only under the influence of estrogens. In the absence of excess estrogens from conditions such as Klinefelter syndrome and liver disease, the vestigial male breast has only larger epithelial ducts.[22] Therefore, the in situ and InvBC morphologic patterns observed in male breast carcinoma resembled those present in the more central ducts of the female breast, which are predominantly of the papillary type.[23] These papillary tumors may be relatively hormone-independent and tend to persist with advancing age.[24,25] Indeed, consistent with hormone-independent carcinogenesis,[26] advancing age was a steady risk factor for male breast carcinoma overall (Fig. 2). In contrast, age-specific incidence rates for female breast carcinoma overall increased rapidly until age 50 years then rose more slowly, suggesting an important etiologic role for carcinogenic events and/or exposures operating before menopause.[27,28]

Advancing age may also explain gender-related differences between overall survival (Fig. 4). Median age at diagnosis was significantly higher ($P < 0.001$) among men compared to women (Tables 2–3), and age-related comorbid illnesses could very possibly im-

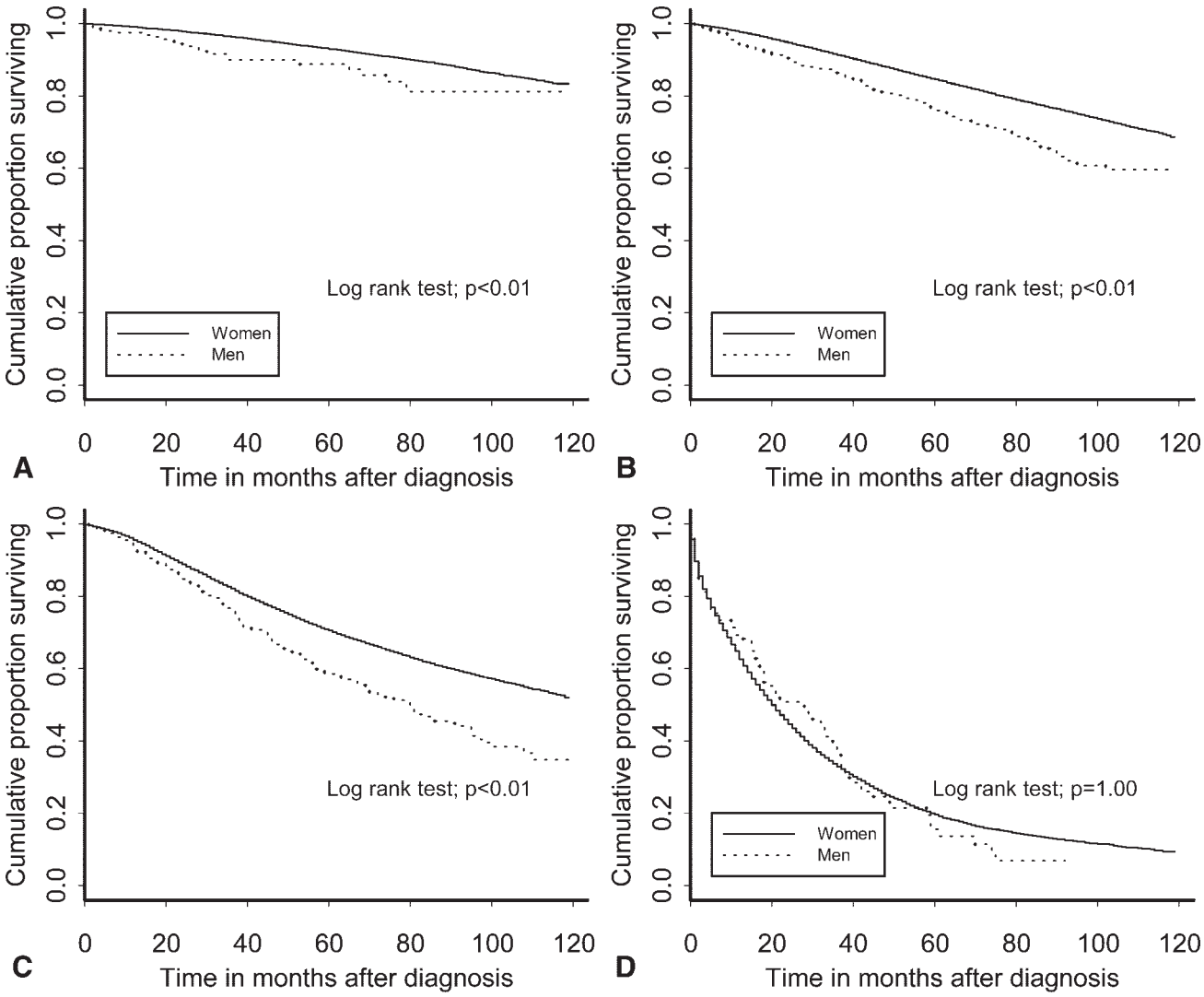

FIGURE 4. SEER historic stage-specific actuarial overall survival (all causes) by gender for the SEER 12 Registry Database during the years 1992–2001. (A) In situ breast carcinoma; (B) Local invasive breast carcinoma; (C) Regional invasive breast carcinoma; (D) Distant invasive breast carcinoma.

pact older men more than younger women.[29] Notwithstanding worse overall survival, breast carcinoma-specific survival was no different for men than for women (Fig. 3), consistent with the relatively favorable tumor characteristics among men (Table 2).

The strength of this study was its large-scale population-based design. Limitations included lack of central pathologic slide review and incomplete and nonstandardized criteria for ER evaluation, possibly making some conclusions suspect. Although the large-scale population-based design of SEER databases should theoretically balance the diagnostic variations among pathologists and laboratories for the 12 SEER registries, future prospective studies may be required to corroborate our retrospective observations. Information regarding method of detection also would have been useful for this in situ breast carcinoma study. However, SEER does not record method of detection, and, of course, all male breast carcinoma would be symptomatically derived.

In summary, in situ male breast carcinoma may provide a conceptual breast carcinoma model apart from female-related reproductive risk factors, hormone exposures, and screening mammography. For example, gender-related differences in histopathologic types suggest an important etiologic role for the estrogen-dependent TDLU, which is absent in men and present in women. Temporal trends suggestive of early detection over time for both genders suggest that screening mammography can not totally account for rising in situ breast carcinoma rates for either men or women. Although rare, continued population-based

surveillance for male breast carcinoma is certainly just as warranted and important as it is for women.

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